Boronate Urea Activation of Strained Rings

Honors Research Thesis

Presented in Partial Fulfillment of the Requirements for graduation "with Honors Research Distinction in Chemistry" in the undergraduate colleges of The Ohio State University

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A. Abstract.

Reactions catalyzed by small organic molecules through non-covalent interactions are emerging as powerful tools for the synthesis of valuable target molecules. Specifically, hydrogen bond donors (HBDs) are useful non-covalent catalysts able to interact with a variety of functional groups and operate in a number of transformations. Boronate ureas have been identified as a new class of HBDs with enhanced reactivity due to the strategic placement of an internal Lewis acid. Specifically, in comparison to conventional ureas, boronate ureas benefit from lower catalyst loadings, reduced reaction times and access to unique reactivity patterns. To this end, we have discovered boronate ureas operate as catalysts for the ring-opening of strained ring systems, giving rise to valuable building blocks in good yield.

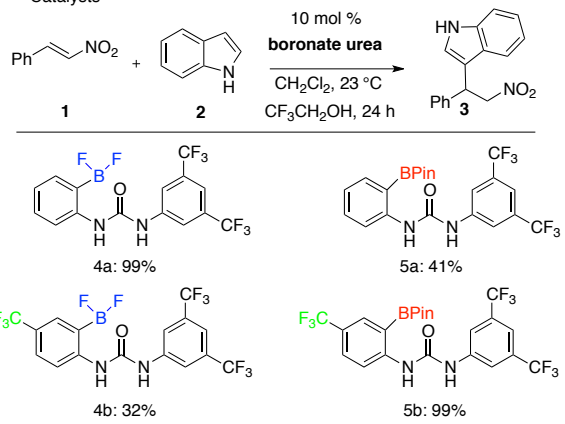
B. Background.

I. Catalysis. Chemical catalysis is a powerful tool in organic synthesis, as it leads to improved efficiency and product conversion in a variety of reactions. While most traditional catalysts center on the properties of transition metals, recent innovations in catalysis have begun utilizing small organic molecules. Features rendering these catalysts particularly useful include their relatively non-toxic and robust nature, low cost, and ability to offer complementary synthetic strategies to transition metal catalysts.

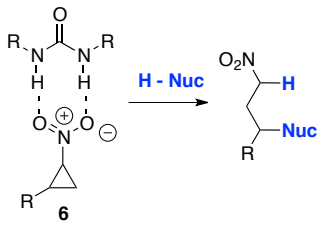
II. Internal Lewis Acid Assisted Hydrogen Bond Donors. Ureas have emerged as valuable dual HBD's for the activation of groups such as carbonyls and nitro groups. Before these

organic catalysts can reach their full potential certain limitations, such as high catalyst loading and limited reaction scopes, must be addressed. One strategy to address these issues includes the development of hydrogen bond donor catalysts with improved activity. To this end, boronate ureas have been identified as a new class of HBDs benefitting from enhanced reactivity due to the strategically placement of an internal Lewis acid.[1] In comparison to conventional HBDs, these catalysts benefit from lower catalyst loadings and reduced reaction times when employed in nucleophilic addition reactions of nitroalkenes (Scheme 1). Boronate urea catalysts (**4** and **5**) have reported improved reactivity in comparison to conventional catalysts in the conjugate addition reaction of indole (**2**) to β-nitrostyrene (**1**).[2] Through similar coordination of the boronate urea hydrogens to a nitrocyclopropane (**6**), we began to explore the possibilities of opening these strained systems under nucleophilic additions to produce highly functionalized products available for a variety of useful transformations (Scheme 2).

Scheme 1: Boronate Ureas as Enhanced Hydrogen Bond Donor Catalysts



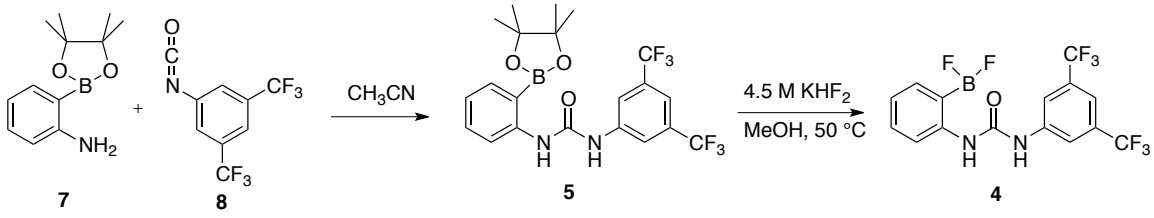
Scheme 2: New Reactivity Mode: Activation of Strained Systems



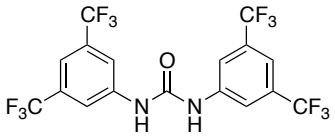
C. Results.

I. Boronate Urea Synthesis. The synthesis of the pinacol ester boronate urea (**5**) began with 2-aminophenyl boronic acid pinacol ester (**7**) dissolved in THF under N_2. The addition of 3,5-*bis*-trifluoromethylphenyl isocyanate (**8**) afforded our original pinacol ester catalyst in good yield (Scheme 3). This product (**5**) was then dissolved in MeOH, where it was heated to 50 °C after the addition of KHF_2 to yield the difluoroboronate catalyst (**4**). These white solid catalysts were easily stored at room temperature with no observable decomposition.

Scheme 3: Generation of Boronate Urea Catalyst



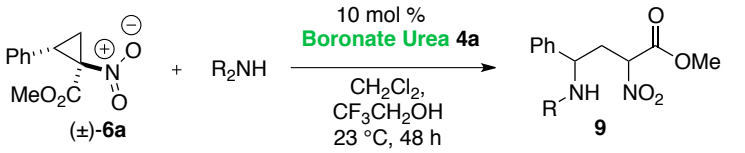
II. Substrate Scope: Nitrogen Nucleophiles. With the promising ring-opening reactions shown with nickel catalysts and nitrogen nucleophiles, we began similar investigations utilizing the boronate urea catalysts.4 In the presence of 10 mol % of boronate urea 4a, anilne underwent nucleophilic addition to racemic nitrocyclopropane **6** giving rise to **9a** in 87% yield as a 1:1 mixture of diastereomers after 48 h at 23 °C in methylene chloride (Table 1). Boronate urea 4a proved to be a more efficient catalyst than convention urea catalyst **10**. The scope of nucleophiles was examined, where we were able to incorporate an array of nitrogen containing molecules (Table 1). Not only were aniline derivatives tolerated with both electron-withdrawing and electron-donating substituents, but nitrogen heterocycles also operated well as nucleophiles in the process.

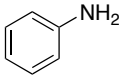
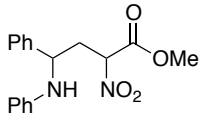
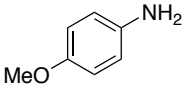
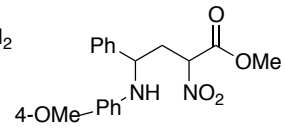
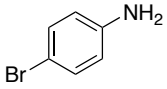
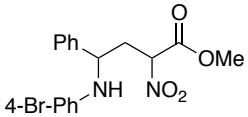
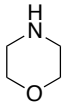
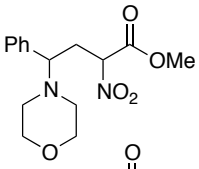
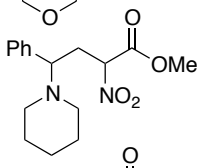
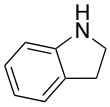
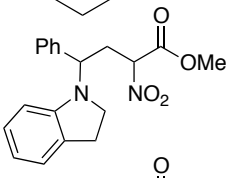
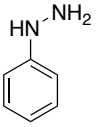
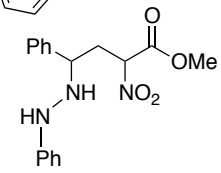


Conventional Urea Catalyst 10

The addition of morpholine, indoline, piperidine, and phenyl hydrazine converted nitrocyclopropane **6** to the corresponding ring-opened products in good yields.

Table 1. Survey of amines in boronate urea catlyzed right opening of 6a[a]



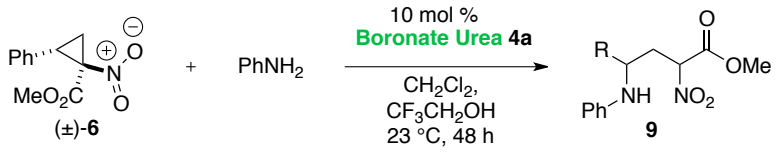
entry	amine	product[b]	yield (%)[c]
1		 **9a**	87
2		 **9b**	90
3		 **9c**	58
4		 **9d**	95
5		 **9e**	78
6[d]		 **9f**	99
7		 **9g**	99

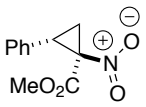
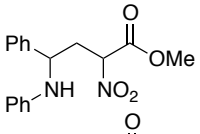
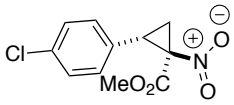
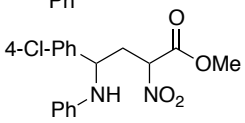
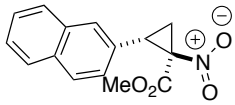
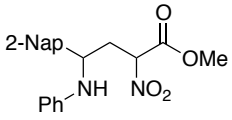
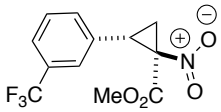
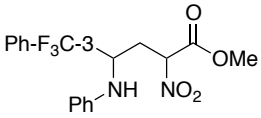
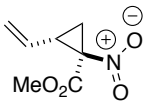
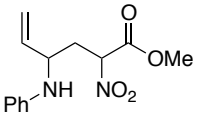
[a] Reactions performed using 1.5 equiv of amine at a concentration of 0.5 M. Control experiments show no reaction is observed in the absense of the urea catlyst.
[b] Isolated as a 1:1 mixture of diastereomers unless otherwise noted [c] Isolated yield
[d] 1:1.3 dr

Once we were able to demonstrate the success of a variety of nucleophiles for this ring-opening reaction, we began exploring the possibilities in substitution patterns on the nitrocyclopropanes. Substituted phenyl rings on the nitrocyclopropane operated as electrophiles in the reaction and we were able to access additional α-nitro esters in good yield (Entries 1-4, Table 2). In addition to employing aromatic rings as substituents, alkenes proved to be suitable substituents for the ring-opening of nitrocyclopropane (Entry 5).

After discovering the tolerance of this reaction, we began investigation on the stereochemical outcomes of the ring-opening reaction by using an enantioenriched nitrocyclopropane. The exposure of enantioenriched **6a** (89% ee) to indoline gave rise to 99% of **5f** as a 1:1 mixture of diastereomers with complete inversion of stereochemistry (91% ee for each of the products). Taking this into consideration, we proposed a plausible catalytic pathway (Scheme 5). Initial coordination of **6a** with **4a** affords the activated nitrocyclopropane intermediate **I**. Nucleophilic attack by the amine causes ring-opening giving rise to **II** through an S_N2-type of reaction pathway, consistent with the observation that the product has inverted stereochemistry with respect to the starting material. After proton transfer (**III**) the product is released with simultaneous reintroduction of the boronate urea into the catalytic cycle.

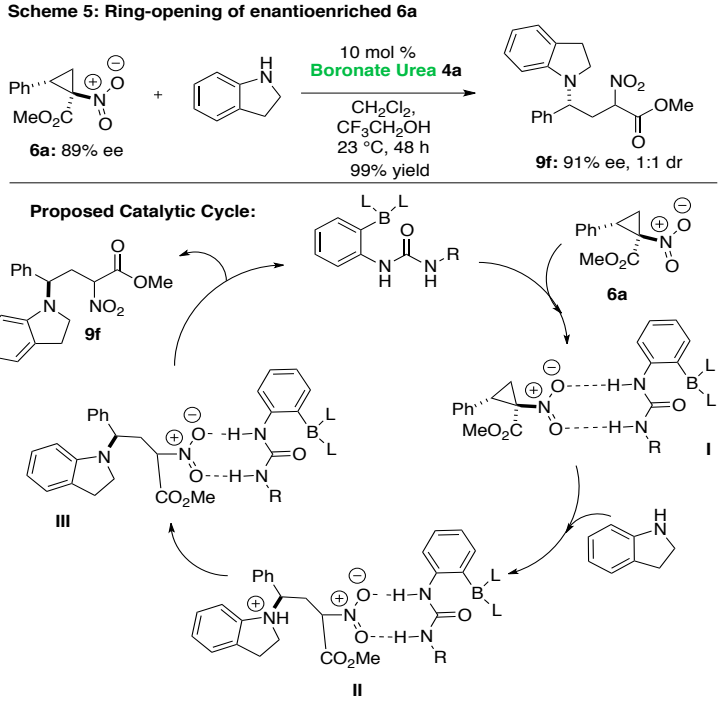
Table 2: Survey of nitrocyclopropanes compatible in boronate urea catalyzed ring-opening reactions[a]



entry	(±)-6	product[b]		yield (%)[c]
1			**9a**	87
2			**9h**	77
3			**9i**	99
4			**9j**	59
5			**9k**	76

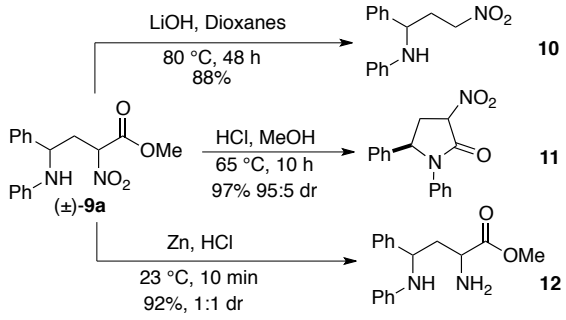
[a] Reactions performed using 1.5 equiv of aniline at a concentration of 0.5 M.
[b] Isolated as a 1:1 mixture of diastereomers [c] Isolated yield

Scheme 5: Ring-opening of enantioenriched 6a



IV. Utility of Ring-Opened Products. To emphasize the synthetic importance of the ring-opened products, some manipulations were performed on product **9a**, as shown in Scheme 6. Decarboxylation with lithium hydroxide in dioxanes gave the amine **10** in high yields. By reacting **9a** with HCl in MeOH, a lactam was produced in high yields, with one diastereomer as shown through NMR spectroscopy techniques.

Scheme 6: Examples of 9a utility

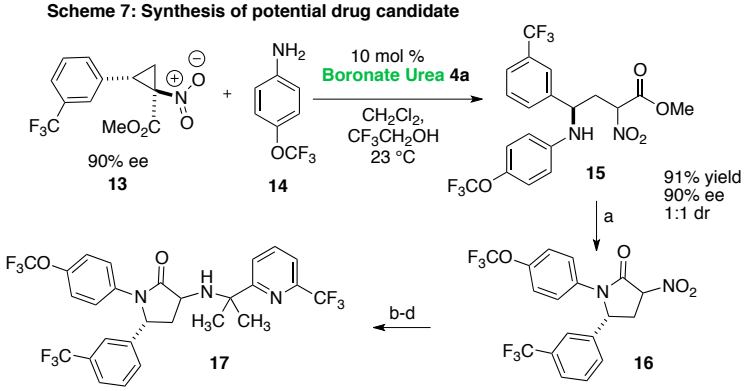


Using zinc and hydrochloric acid, the nitro group on the ring-opened product was reduced to give the free amine in good yields with a 1:1 diastereomeric ratio.

To further illustrate the synthetic utility of these products, we proceeded to manipulate our substrates to create a molecule of biological importance. Based off the potential transformations we were able to accomplish, we began investigation towards

synthesizing a CB-1 receptor inverse agonist that was recently patented by Eli Lilly (scheme 7).[5] By using an enantiopure cyclopropane, we added 4-(trifluoromethoxy)-aniline (**14**) to create our ring-opened product (**15**). Using our procedure to transform this product into the lactam, we created the corresponding lactam for this particular product (**16**) in high yields. After reducing the nitro-group into an amine and performing an imine condensation with 1-(6-(trifluoromethyl)pyridin-2-yl)ethanone, the addition of trimethylaluminum afforded our final drug target (**17**).

Scheme 7: Synthesis of potential drug candidate



a) Hcl, MeOH, 65 °C, 97%, 1:1 dr; b) Zn, HCl, 92%; c) 1-(6-(trifluoromethyl)pyridin-2-yl)ethanone, CSA; d) $AlMe_3$, 43% for 2 steps

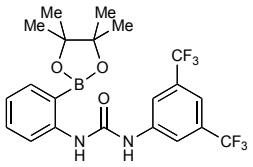
D. Conclusions

Boronate ureas operate as enhanced hydrogen bond donor catalysts for nucleophilic ring-opening reactions of nitrocyclopropane carboxylates. A variety of amine nucleophiles and nitrocyclopropanes were well tolerated in the process giving rise to useful a-nitro ester building blocks. The methodology was incorporated into a synthesis of a bioactive g-lactam with industrial interest.

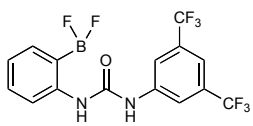
F. Experimental Procedures

General Methods. Benzene was freshly distilled from sodium and methanol was freshly distilled from CaH_2 prior to use. Methylene chloride was purified by passage through a bed of activated alumina.[6] Purification of reaction products was carried out by flash chromatography using Aldrich 60 Å (40-63 μm). Analytical thin layer chromatography was performed on EMD Chemicals 0.25 μm silica gel 60-F_{254} plates. Visualization was accomplished with UV light and potassium permanganate or ceric ammonium molybdate stains followed by heating. Melting points (**mp**) were obtained on a Thermo Scientific Mel-temp apparatus and are uncorrected. Infrared spectra (**IR)** were obtained on a Perkin Elmer Spectrum 100R spectrophotometer. Infrared spectra for liquid products were obtained as a thin film on a NaCl disk, and spectra for solid products were collected by preparing a NaBr pellet containing the title compound. Proton nuclear magnetic resonances (**^{1}H NMR**) were recorded in deuterated solvents on a Bruker Avance DPX 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm, δ) using the solvent as internal standard ($CHCl_3$, δ 7.26 and DMSO, δ 2.50) ^{1}H NMR splitting patters are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Coupling constants are reported in Hertz (Hz). Proton-decoupled carbon (**^{13}C-NMR**) spectra were recorded on a Bruker Avance DPX 400 (100 MHz) spectrometer and are reported in ppm using the solvent as an internal standard ($CHCl_3$, δ 77.0 and DMSO, δ 39.5).

Typical Procedure for generation of Boronate Urea HBD's



Synthesis of pinacol ester boronate urea 5[7]: A flame-dried round bottom flask under N_2 was charged with 2-aminophenyl boronic acid pinacol ester (600 mg, 2.74 mmol). Acetonitrile (30 mL) was added to create a clear and colorless solution. Last, the 3,5-*bis*-trifluoromethylphenyl isocyanate (2.74 mmol) was introduced to the reaction flask dropwise by syringe. Shortly after addition of the isocyanate a white precipitate began to form. The reaction was allowed to stir at 23 ˚C for 4 h. The pure boronate urea pinacol ester was isolated as a white solid after vacuum filtration followed by washing with cold acetonitrile. The solid was dried under vacuum (83%). R_f = 0.94 (4:4:1 ethyl acetate/hexanes/methanol); mp 215.2 – 216.9 ˚C; IR (NaBr) 3415, 3132, 2985, 1640, 1600, 1581, 1476, 1184, 1129, cm^{-1}; ^1H NMR (400 MHz, DMSO d_6) δ 9.93 (br s, 1H); 9.19 (br s, 1H); 8.16 (s, 2H); 7.69 (s, 1H); 7.52-7.50 (m, 1H); 7.42-7.34 (m, 2H); 7.08-7.04 (m, 1H); 1.24 (s, 12H); ^{13}C NMR (100 MHz, DMSO d_6) δ 154.0, 142.2, 141.7, 134.7, 131.2 (q, J = 6 Hz, CF_3), 155.61-155.5 (m), 83.0, 25.5 (the carbon bonded to boron was not seen due to broadening)[8]; ^{11}B NMR (160 MHz, DMSO d_6) δ26.0 (br s); HRMS (ESI): Mass calculated for $C_{21}H_{21}BF_6N_2O_3$ $[M+H]^+$, 475.1622. Found $[M+H]^+$, 475.1614.

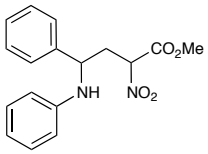


Synthesis of difluoroboronate urea 4:[9] A flame-dired flask under N_2 was charged with a boronate urea pinacol ester (4.6 mmol). MeOH (30 mL) was added. Last, KHF_2 (4.5 M, 18.4 mmol) was introduced to the reaction flask dropwise by syringe, resulting in a white

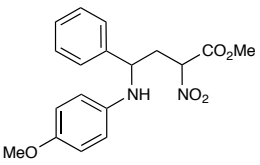
heterogeneous mixture, and the reaction was heated to 50 ˚C. Shortly after heating, the reaction became a clear and colorless solution. After 2 h at 50 ˚C, the reaction was cooled to 23 ˚C and concentrated. The white solid was filtered and washed several times with water to afford the potassium trifluoroboryl urea salt (92%). The urea (1.95 g, 4.29 mmol) was dissolved in ethyl acetate (15 mL) and extracted twice with water (5 mL). The organic later was dried and concentrated to afford a white solid, which was then dissolved in a minimal volume of hot acetonitrile. The solution was allowed to cool to room temperature and then placed in an ice bath. The precipitate was filtered off and the filtrate was concentrated to afford the difluoroboryl urea (NUMBER) (1.23 g, 3.11 mmol, 72%) as a white powder. R_f = 0.74 (4:4:1 ethyl acetate/hexanes/methanol); mp 205.3-205.9 ˚C; IR (NaBr) 3628, 3345, 2986, 1741, 1671, 1585, 1479, 1187, 1128, cm^{-1}; ^1H NMR (400 MHz, DMSO, d_6) δ 11.27 (br s, 1H); 10.65 (br s, 1H); 8.11 (s, 2H); 7.96 (s, 1H); 7.42-7.40 (m, 1H); 7.32-7.28 (m, 1H); 7.15-7.10 (m, 1H); 1.24; ^{13}C NMR (100 MHz, DMSO, d_6) δ 154.5, 138.1, 137.4, 131.5, 131.2, 130.9, 130.6, 128.2, 124.7, 123.0 (q, J = 267 Hz, CF_3), 118.4, 115.4; ^{11}B NMR (160 MHz, DMSO d_6) δ 3.63 (br, s); ^{19}F NMR (376 MHz, DMSO d_6) δ -61.7 (s, 6F), -132.8 (s, 1F), -132.9 (s, 1F); HRMS (ESI): Mass calculated for $C_{21}H_{21}BF_6N_2O_3$ $[M+H]^+$, 419.0572. Found $[M+H]^+$, 419.0580.

Typical Procedure for the Addition of Nitrogen-based Nucleophiles to Nitrocyclopropanes: A dry, screw-capped reaction vial containing a magnetic stir bar was charged with nitrocyclopropane (0.170 mmol) and then catalyst (10 mol %). The reaction was fitted with cap and septum and put under a positive pressure of N_2. Methylene chloride (0.340 mL, 0.50 M) was added followed by amine nucleophile (0.255

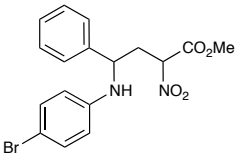
mmol) and trifluoroethanol (12.2 μL, 0.170 mmol). The reaction was allowed to stir for 48 hours. The reaction was immediately purified by flash column chromatography on silica gel.



9a: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 48.6 mg (87%, 1:1 dr) of **9a** as a light yellow solid. R_f = 0.19 (20:80 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.39-7.26 (m, 10H); 7.14-7.09 (m, 4H); 6.71 (t, *J* = 8 Hz, 2H); 6.58-6.55 (m, 4H); 5.44 (dd, *J* = 8.0, 4.0 Hz, 1H); 5.13 (dd, *J* = 8.0, 4.0 Hz, 1H); 4.56-4.48 (m, 2H); 4.03-4.01 (m, 2H); 3.83 (s, 3H); 3.80 (s, 3H); 2.91-2.65 (m, 2H); 2.63-2.55 (m, 2H). All spectral data match those previously reported.[10]

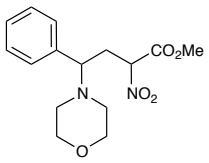


9b: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 52.7 mg (90%, 1:1 dr) of **9b** as a white solid. R_f = 0.21 (20:80 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CHCl_3$, mixture of two diastereomers) δ 7.38-7.24 (m, 1H); 5.15 (dd, *J* = 5.2, 8.8 Hz, 1H); 4.44-4.40 (m, 2H); 3.82 (s, 3H); 3.80 (s, 3H); 3.75 (br s, 2H); 3.70 (s, 3H); 2.86-2.77 (m, 2H); 2.63-2.53 (m, 2H). All spectral data match those previously reported.[10]

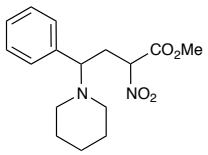


9c: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 38.8 mg (58%, 1:1 dr) of **9c** as a light yellow oil. R_f = 0.2 (20% ethyl

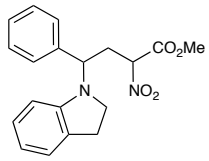
acetate/hexanes); FTIR (film) 3055, 2987, 2306, 1756, 1565, 1423, 1265, 896, 738; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.41-7.28 (m, 10H); 7.26-7.20 (m, 4H); 6.48-6.45 (m, 4H); 5.45-5.41 (m, 1H); 5.15-5.12 (m, 1H); 4.52-4.45 (m, 1H); 4.14-4.12 (m, 1H); 3.85 (s, 3H); 3.82 (s, 3H); 2.92-2.81 (m, 2H); 2.66-2.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two diastereomers) δ 165.1, 164.7, 145.3, 145.2, 140.6, 140.3, 132.1, 132.00, 131.97, 129.3, 129.1, 128.3, 126.3, 125.9, 115.6, 115.4, 110.4, 110.2, 55.3, 54.8, 53.8, 38.4, 37.8; HRMS (ESI): Mass calculated for $C_{17}H_{17}BrN_2O_4$ $[M]^+$, 415.0264 Found $[M+Na]^+$, 415.0273.



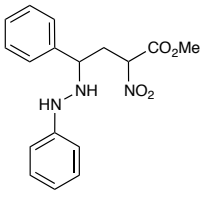
9d: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 48.5 mg (95%, 1:1 dr) of **9d** as a light yellow oil. R_f = 0.2 (20:80 ethyl acetate/hexanes); FTIR (film) 3054, 2987, 2305, 2254, 1755, 1564, 1438, 1265, 117, 910. ^{1}H NMR (400 MHZ, $CDCl_3$, mixture of two diastereomers) δ 7.38-7.32 (m, 6H); 7.18-7.13 (m, 4H); 5.54 (dd, *J* = 4.0, 8.0 Hz, 1H); 5.09 (dd, *J* = 4.0, 8.0 Hz, 1H); 3.85 (s, 3H); 3.79 (s, 3H); 3.68-3.62 (m, 8H); 3.52-3.49 (m, 1H); 3.44-3.42 (m, 1H); 3.13-3.05 (m, 1H); 2.96-2.89 (m, 1H); 2.58-2.38 (m, 6H); 2.35 (m_c, 2H); 2.26 (m_c, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two diastereomers) δ 165.5, 165.2, 136.3, 135.4, 128.6, 128.5, 128.4, 128.34, 128.3, 128.25, 128.2, 86.5, 67.2, 67.1, 66.9, 65.6, 53.6, 50.4, 49.6, 32.5, 31.9; HRMS (ESI): Mass calculated for $C_{15}H_{20}N_2O_5$ $[M+H]^+$, 309.1445 Found $[M+H]^+$, 309.1435.



9e: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 42.5 mg (78%, 1:1 dr) of **9e** as a light yellow oil. R_f = 0.18 (20:80 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.37-7.30 (m, 6H); 7.16-7.15 (m, 4H); 5.65 (br s, 1H); 5.32-5.22 (br m, 1H); 3.85 (s, 3H); 3.80 (s, 3H); 3.58-3.56 (br m, 2H); 3.15-3.09 (m, 1H); 3.07-2.94 (m, 1H); 2.51-2.43 (br m, 4H); 2.18-2.13 (br m, 4H); 1.51-1.49 (br s, 8H); 1.30-1.28 (br m, 2H). All spectral data match those previously reported.[10]

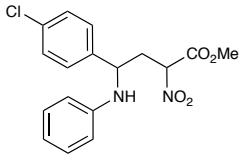


9f: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 57.8 mg (99%, 1:1 dr) of **9f** as a light yellow solid. R_f = 0.2 (20:80 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 10H); 7.09-7.02 (m, 4H); 6.67-6.63 (m, 2H); 6.59-6.57 (m, 2H); 5.49-5.46 (m, 1H); 5.24 (t, J = 6.8 Hz); 4.90-4.88 (m, 1H); 4.86-4.84 (m, 1H); 3.79 (s, 3H); 3.41-3.35 (m, 2H); 3.11-3.03 (m, 3H); 3.01-2.80 (m, 7H). All spectral data match those previously reported[10]

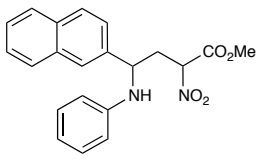


9g: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 55.4 mg (99%, 1:1 dr) of **9g** as a light yellow oil. R_f = 0.18 (20:80 ethyl acetate/hexanes); FTIR (film): 3054, 2987, 2305, 2254, 1600, 1564, 1422, 1266, 909, 739, 467; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.31-7.24 (m, 13H); 7.20-7.17 (m, 2H); 6.98-6.88 (m, 5H); 5.65 (dd, J = 9.8, 4.4 Hz, 1H); 5.39 (t, J = 6.6 Hz,

1H); 5.13 (dd, *J* = 10.3, 5.0 Hz, 1H); 4.92 (dd. *J* = 11.6, 3.5 Hz, 1H); 3.83 (s, 3H); 3.81 (s, 3H); 3.45-3.37 (m, 2H); 2.85-2.75 (m, 2H); ^{13}C NMR (100 MHz, CDCl3, mixture of two diastereomers) δ 165.5, 165.2, 151.6, 151.3, 136.6, 136.2, 129.2, 128.5, 128.4, 128.2, 127.8, 127.8, 120.2, 119.8, 115.1, 114.5, 86.0, 85.9, 62.0, 61.7, 53.6, 53.6, 32.6, 32.3; HRMS (ESI): Mass calculated for $C_{15}H_{20}N_2O_5$ $[M+H]^+$, 330.1448. Found $[M+H]^+$, 330.1438.

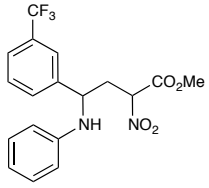


9h: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 46.8 mg (77%, 1:1 dr) of **9h** as a light yellow solid. R_f = 0.18 (20:80 ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.35-7.24 (m, 8H); 7.14-7.10 (m, 4H); 6.74-6.71 (m, 2H); 6.54-6.52 (m, 4H); 5.45 (dd, *J* = 4.8, 8.8 Hz, 1H); 5.15 (dd, *J* = 5.2, 8.0, Hz, 1H); 4.53-4.49 (m, 2H); 4.01 (br s, 2H); 3.83 (s, 3H); 3.81 (s, 3H); 2.84-2.77 (m, 2H); 2.63-2.52 (m, 2H). All spectral data match those previously reported.[10]

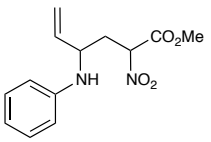


9i: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 61.3 mg (99%, 1:1 dr) of **9i** as a light yellow oil. R_f = 0.2 (20:80 ethyl acetate/hexanes). FTIR (film): 3054, 2987, 1756, 1603, 1564, 1422, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.90−7.78 (m, 8H); 7.53-7.44 (m, 6H); 7.15-7.11 (m, 4H); 6.74-6.62 (m, 2H); 5.52-5.48 (m, 4H); 5.50 (dd, *J* = 8.8, 5.2 Hz, 1H); 5.18 (dd, *J* = 8.8, 5.2 Hz, 1H); 4.74-4.67 (m, 2H); 4.16-4.15 (m, 2H); 3.85 (s, 3H);

3.81 (s, 3H); 3.01-2.92 (m, 2H); 2.77-2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two diastereomers) δ 165.3, 164.9, 146.3, 138.6, 138.2, 133.4, 133.2, 133.0, 129.4, 129.3, 129.2, 128.0, 128.0, 127.7, 127.7, 126.6, 126.5, 126.3, 126.2, 125.6, 125.0, 123.8, 118.7, 118.6, 114.1, 113.9, 85.5, 85.4, 76.7, 55.5, 54.9, 53.8, 53.8, 38.6, 38.0.



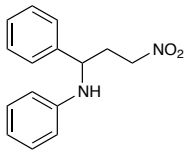
9j: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 38.3 mg (59%, 1:1 dr) of **9j** as a light yellow oil. R_f = 0.2 (20:80 ethyl acetate/hexanes).FTIR (film): 3053, 2986, 1756, 1565, 1265; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.61−7.45 (m, 8H); 7.13 (t, *J* = 8.0 Hz, 4H); 6.76-6.72 (m, 2H); 6.55-6.53 (m, 4H); 5.48 (dd, *J* = 8.0, 4.0 Hz, 1H); 5.20 (dd, *J* = 8.0, 4.0 Hz, 1H); 4.66-4.57 (m, 2H); 4.09-4.05 (m, 2H); 3.84 (s, 3H); 3.82 (s, 3H); 2.88-2.77 (m, 2H); 2.70-2.64 (m, 1H); 2.61-2.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two diastereomers) δ 165.1, 164.6, 145.7, 145.7, 142.6, 142.4, 131.5 (q, *J* = 26.0 Hz, CF_3), 129.7, 129.6, 129.4, 129.4, 129.4, 125.19, 125.2-124.8 (m), 123.0-122.5 (m), 119.0, 118.9, 114.0, 113.8, 85.3, 85.2, 55.0, 54.4, 53.8, 53.8, 38.5, 38.1. HRMS (ESI): Mass calculated for $C_{18}H_{17}F_3N_2NaO_4$ $[M+Na]^+$, 405.1033. Found $[M+Na]^+$, 405.1034.



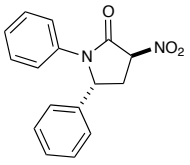
9k: Purified by column chromatography on silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes), yielding 34.1 mg (76%, 1:1 dr) of **9k** as a white solid. Rf = 0.25 (20:80 ethyl acetate/hexanes). 1H NMR (400 MHz, CDCl3, mixture of two diastereomers) δ 7.19−7.16 (m, 4H); 6.77- 6.73 (m, 2H); 6.62-6.59 (m, 4H); 5.80-5.71 (m, 2H); 5.45 (dd, *J*

= 8.8, 4.9 Hz, 1H); 5.32 (dd, *J* = 8.3, 5.5 Hz, 1H); 5.27-5.26 (m, 1H); 5.24-5.22 (m, 2H); 5.22-5.18 (m, 2H); 4.03-4.00 (m, 2H); 3.82 (s, 3H); 3.82 (s, 3H); 3.55 (br s, 2H); 2.70-2.47 (m, 2H); 2.46-2.36 (m, 2H). All spectral data match those previously reported.[10]

General procedure for ring-opened product transformations:

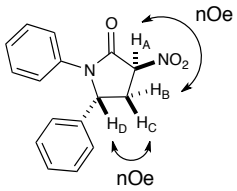


10: A 10 mL round bottom flask equipped with a magnetic stirbar was charged with **9a** (50.0 mg, 0.159 mmol) and LiOH•H_2O (10.0 mg, 0.239 mmol). The mixture was dissolved in 2:1 dioxanes:H_2O (2 mL) and heated to 80 °C for 48 h. The reaction was then neutralized with 1M HCl, extracted with CH_2Cl_2, and dried over Na_2SO_4. The product was purified by column chromatography on silica gel (15:85 ethyl acetate/hexanes) yielding 35.9 mg (88%) of **10** as a white solid, mp 74.6- 76.8 °C. R_f = 0.30 (20:80 ethyl acetate/hexanes); FTIR (film): 3418, 3054, 2986, 1602, 1555, 1382 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38−7.26 (m, 5H); 7.12 (t, *J* = 8.0 Hz, 2H); 6.70 (t, *J* = 8.0 Hz, 1H); 6.57 (d, *J* = 8.0 Hz, 2H); 4.54-4.39 (m, 3H); 4.04 (br s, 1H); 2.61-2.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 141.6, 129.3, 129.1, 127.9, 126.2, 118.3, 113.8, 72.6, 55.5; 35.2; HRMS (ESI): Mass calculated for $C_{15}H_{17}N_2O_2$ $[M+H]^+$, 257.1285. Found $[M+H]^+$, 257.1284.[10]

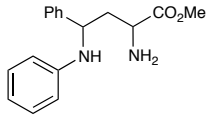


11: A 10 mL round bottom flask equipped with a magnetic stirbar was charged with **9a** (50.0 mg, 0.159 mmol) and dissolved in MeOH (1.59 mL, 0.1 M). Aqueous 1M HCl (1.20 mL, 1.20 mmol) was added and the solution was heated to 65 °C for 12 h. The reaction mixture was then extracted with

CH_2Cl_2, dried over Na_2SO_4, and concentrated. The pure product, **11**, was obtained as a white solid (43.5 mg, 97%, >20:1 dr). R_f = 0.2 (50:50 ethyl acetate/hexanes); FTIR (film): 3054, 2987, 1719, 1562, 1422, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 9H); 7.14-7.12 (m, 1H); 5.57 (t, *J* = 9.2 Hz, 1H); 5.26 (t, *J* = 7.2 Hz); 3.27-3.20 (m, 1H); 2.90-2.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 140.2, 137.4, 129.0, 128.7, 128.5, 127.8, 126.6, 125.2, 123.0, 60.2, 53.6, 40.0; HRMS (ESI): Mass calculated for $C_{16}H_{14}N_2NaO_3$ $[M+Na]^+$, 305.0897. Found $[M+Na]^+$, 305.0908.[11]



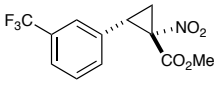
A NOESY experiment was used as a preliminary means to assign the stereochemistry of the major diastereomer obtained for the nitrolactam **11**. The *trans* orientation of the substituents on the nitrolactam ring was assigned based on nOe signals observed between proton H_A/H_B and H_C/H_D. Efforts are ongoing in our laboratory to obtain a crystal structure to confirm this assignment.



12: A 10 mL round bottom flask equipped with a magnetic stirbar was charged with **9a** (50.0 mg, 0.159 mmol) and dissolved in MeOH (1.59 mL, 0.1 M). Concentrated HCl (312 µL, 3.18 mmol) was added and the solution became transparent. The reaction was placed in a 23 °C water bath and zinc powder (417.9 mg, 6.39 mmol) was added with vigorous stirring. After 10 minutes, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and then filtered through celite. The

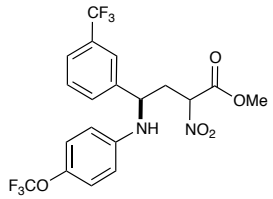
resulting solution was extracted three times with CH_2Cl_2 and dried over Na_2SO_4. The product was purified by column chromatography on silica gel (80:20 ethyl acetate/hexanes to 100% ethyl acetate) yielding 41.4 mg (92%, 1:1 dr) of **12** as a white solid. FTIR (film): 3385, 3054, 2986, 1735, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.43-7.41 (m, 2H); 7.37-7.30 (m, 6H); 7.24-7.21 (m, 2H); 7.11-7.07 (m, 4H); 6.66-6.61 (m, 2H); 6.56-6.52 (m, 4H); 4.74 (dd, *J* = 8.0, 4.0 Hz, 1H); 4.58 (dd, *J* = 8.0, 4.0 Hz, 1H); 3.71 (s, 3H); 3.69 (s, 3H); 3.60 (dd, *J* = 8.0, 4.0 Hz, 1H); 3.52 (dd, J = 12.0, 4.0 Hz, 1H); 2.25-2.19 (m, 2H); 2.05-1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two diastereomers) ™ 176.3, 176.1, 147.6, 147.2, 143.7, 143.1, 129.1, 129.0, 128.7, 128.6, 127.2, 127.0, 126.3, 126.3, 117.3, 117.1, 113.6, 113.2, 57.7, 55.2, 53.4, 52.2, 52.1, 51.9, 42.6, 42.4; HRMS (ESI): Mass calculated for $C_{17}H_{21}N_2O_2$ $[M+H]^+$, 285.1598. Found $[M+H]^+$, 285.1597.[12]

Synthesis of CB-1 receptor inverse agonist[13]

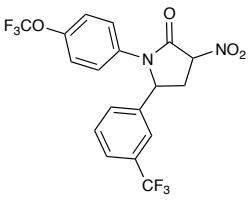


13: The nitrocyclopropane was prepared following the literature procedure.[14] The product was purified by column chromatography on silica gel (hexanes to 5% diethyl ether in hexanes) yielding **13** (21% yield, 90% ee) as a colorless liquid. R_f = 0.2 (5:95 ethyl acetate/hexanes); FTIR (film): 3474, 3058, 2958, 1748, 1550, 1440, 1200, 1130, 1074, 895, 740, 464; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 4.0 Hz, 1H); 7.48-7.41 (m, 3H); 3.80 (t, *J* = 12 Hz, 1 H); 3.54 (s, 3H); 2.47 (dd, *J* = 8.0, 4.0 Hz, 1H); 2.28 (dd, *J* = 8.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 133.3, 131.9, 131.1 (q, *J* = 30 Hz, CF_3), 129.1, 125.3 (q, 4.0 Hz, CF_3), 125.1 (q, 4.0 Hz,

CF_3), 122.4, 71.4, 53.3, 33.3, 20.7; HRMS (ESI): Mass calculated for $C_{12}H_{10}F_3NO_4Na$ $[M+Na]^+$, 312.0454. Found [M+Na]+, 312.0445. $[\alpha]_D^{23} = -39.4°$ (*c* 2.7, $CHCl_3$). HPLC (OD-H Chiralcel, 1% IPA in hexanes, 1.5 mL/min) tr 6.6 min (major), tr 7.1 min (minor).

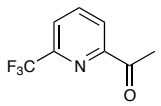


15: The nitrocyclopropane opening of **13** with 4-(trifluoromethoxy)aniline (**14)** was conducted following the above procedure. The product was purified by column chromatography on silica gel (5:95 diethyl ether/hexanes) yielding 72.1 mg (91%) of **15** as a yellow oil. R_f = 0.18 (20:80 ethyl acetate/hexanes); FTIR (film): 3055, 2987, 2685, 1515, 1422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.56 (m, 4H); 7.53-7.49 (m, 4H) 6.98 (d, *J* = 8.0 Hz, 4H); 6.50 (d, *J* = 8.0 Hz, 4H); 5.46 (dd, *J* = 8.0, 4.0 Hz, 1H); 5.18 (dd, *J* = 8.0, 4.0 Hz, 1H); 4.59-4.53 (m, 2H); 4.22-4.16 (m, 2H); 3.84 (s, 3H); 3.82 (s, 3H); 2.87-2.78 (m, 2H); 2.69-2.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 164.6, 144.5, 142.2, 141.9, 141.56-141.49 (m), 131.8 (d, *J* = 6.0 Hz), 131.2 (d, *J* = 6.0 Hz), 129.8, 129.8, 129.7, 129.4, 125.2-125.0 (m), 123.0-122.5 (m), 122.2, 121.8, 119.3, 114.4, 114.2, 85.3, 85.1, 55.3, 54.8, 53.9, 38.4, 38.0; HRMS (ESI): Mass calculated for $C_{19}H_{16}F_6N_2NaO_5$ $[M+Na]^+$, 489.0856. Found $[M+Na]^+$, 489.0876. $[\alpha]_D^{23} = -11.1°$ (*c* 1, MeOH).



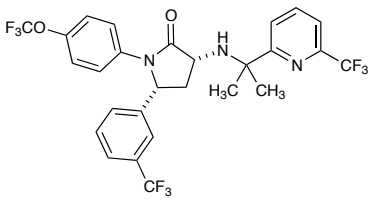
16: To a 100 mL round bottom flask equipped with stirbar was added 300 mg (0.643 mmol) followed by freshly distilled methanol (15 mL) under Ar. Dilute HCl (15 mL, 1M) was added and a white precipitate formed. Upon heating to 65 °C for 12 h, the precipitate dissolved

and formed a brown oil. The reaction was cooled and extracted three times with CH_2Cl_2. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated. The product was obtained as a light yellow oil as a 1:1 mixture of diastereomers (251.3 mg, 90%) and used without further purification. R_f = 0.6 (45:55 ethyl acetate/hexanes); FTIR (film): 3054, 2987, 1725, 1565, 1510, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.48 (m, 7H); 7.42-7.35 (m, 5H); 7.26-7.11 (m, 4H); 5.63-5.54 (m, 3H); 5.35-5.31 (m, 1H); 3.40-3.28 (m, 2H); 2.87-2.79 (m, 1H); 2.59-2.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two diastereomers) δ 163.9, 163.8, 147.2, 147.1, 139.7, 139.5, 134.7, 134.2, 132.1 (q, J = 33 Hz, CF_3), 131.7 (q, J = 33 Hz, CF_3), 130.3, 130.2, 129.8, 129.2, 125.9 (q, J = 3 Hz, CF_3), 124.9, 124.9, 124.8, 124.1, 123.8 (q, J = 5 Hz, CF_3), 123.1-123.0 (m), 122.2, 122.2, 121.7, 121.6, 119.0, 119.0, 85.2, 85.1, 61.7, 60.4, 34.8, 33.8; HRMS (ESI): Mass calculated for $C_{18}H_{12}F_6N_2NaO_4^+$ $[M+Na]^+$, 457.0593. Found $[M+Na]^+$, 457.0571. $[\alpha]_D^{23}$ = –32.6° (*c* 1.46, $CHCl_3$).



1-(6-(trifluoromethyl)pyridin-2-yl)ethanone: A flame-dried 100 mL round bottom flask was charged with 2-bromo-6-trifluoromethyl pyridine (1.50 g, 6.64 mmol, ordered from Combi-blocks) under Ar. Dry diethyl ether (30 mL) was added and the flask was then cooled to –78 °C. Dropwise addition of 1.6 M *n*BuLi (4.56 mL, 7.30 mmol) occurred over 25 minutes. Freshly distilled dimethyl acetamide (0.617 mL, 6.64 mmol) was added dropwise and the reaction was allowed to warm to room temperature overnight. Water (25 mL) was added to quench the reaction and was then extracted 3 times with dichloromethane. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated to yield a light brown oil. The compound was

further purified by flash column chromatography (20:80 ethyl acetate/hexanes) yielding 0.59 g (47%) of **1-(6- (trifluoromethyl)pyridin-2-yl)ethanone** as a colorless liquid. FTIR (film): 3053, 2986, 2305, 2254, 1703, 1422, 1265, 910, 737, 651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.0 Hz, 1H); 8.02 (t, J = 7.6 Hz, 1H); 7.84 (d, J = 7.6 Hz, 1H); 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 153.5, 147.7 (q, J = 35 Hz, CF_3), 138.5, 123.6, 123.5, 121.1 (q, J = 273 Hz, CF_3), 25.5; HRMS (ESI): Mass calculated for $C_8H_6F_3NNaO^+$ $[M+Na]^+$, 212.0294. Found $[M+Na]^+$, 212.0293.[15]



17: To a 25 mL flame-dried round bottom flask equipped with stirbar was added 1-(6-(trifluoromethyl)pyridin-2-yl)ethanone (136 mg, 0.717 mmol) under Ar. Freshly distilled toluene (10 mL) was added followed by aminolactam **16** (290 mg, 0.717 mmol). A catalytic amount of camphor sulfonic acid (10 mg) and 4Å molecular sieves were added (100 mg). The reaction was allowed to stir at 85 °C for 48 hours. Upon cooling, the mixture was concentrated and then purified by flash column chromatography using basic alumina (20:80 diethyl ether/hexanes to 50:50 diethyl ether/hexanes). The imine product was obtained as a light yellow oil (268 mg, 65%) and used without further purification. 1-(4-(trifluoromethoxy)phenyl)-5-(3- (trifluoromethyl)phenyl)-3-(1-(6-(trifluoromethyl)pyridin-2-yl)ethylidene)amino)pyrrolidin-2- one (50 mg, 0.087 mmol) was added to a flame dried round bottom flask equipped with stirbar under Ar. Freshly distilled toluene (4 mL) was added and the flask was cooled to 0 °C. Dropwise addition of $AlMe_3$ (0.13 mmol, 2.0 M in hexanes) occurred over 5 minutes. The solution turned deep red and was allowed to stir for 12 h. The reaction was quenched with H_2O (5 mL)

and the solution turned yellow. The solution was extracted three times with ethyl acetate. **17** was obtained as a 1:1 mixture of diastereomers (43%) by flash column chromatography using silica gel (50:50 diethyl ether/hexanes).

Cis diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.80 (m, 2H); 7.52-7.48 (m, 1 H); 7.47- 7.40 (m, 1H); 7.39-7.31 (m, 3H); 7.25-7.20 (m, 2H); 7.05-7.01 (m, 1H); 5.03 (dd, *J* = 8.0, 4.0 Hz, 1H); 3.48 (dd, *J* = 10.8, 2.8 Hz, 1H); 2.81-2.77 (m, 1H); 1.88-1.79 (m, 1H); 1.56 (s, 3H); 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.7, 167.1, 140.8, 137.7, 131.7, 129.9, 129.8, 124.9, 123.6, 122.9, 122.0, 121.9, 121.3, 118.2, 115.9, 60.1, 58.7, 55.4, 30.0, 29.7; HRMS (ESI): Mass calculated for $C_{27}H_{22}F_9N_3O_2$ $[M+H]^+$, 592.1641. Found $[M+H]^+$ 592.1632.

Trans diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.78 (m, 2); 7.54-7.50 (m, 4H); 7.44- 7.41 (m, 1H); 7.37 (s, 1H); 7.24-7.28 (m, 1H); 7.12-7.11 (m, 2H); 5.18 (d, *J* = 8.5 Hz, 1H); 3.66 (dd, *J* = 10.5, 8.0 Hz, 1H); 2.48-2.42 (m, 1H); 2.26-2.22 (m, 1H); 1.56 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 167.1, 147.1 (q, *J* = 34 Hz, CF_3), 145.9, 141.6, 137.8, 136.7, 131.8 (q, *J* = 34 Hz, CF_3), 129.8, 128.4, 124.9-124.8 (m), 124.1, 122.7, 122.6-122.5 (m), 122.0, 121.5, 120.4, 119.4, 118.18, 60.5, 58.3, 53.3, 40.4, 29.3, 27.9.

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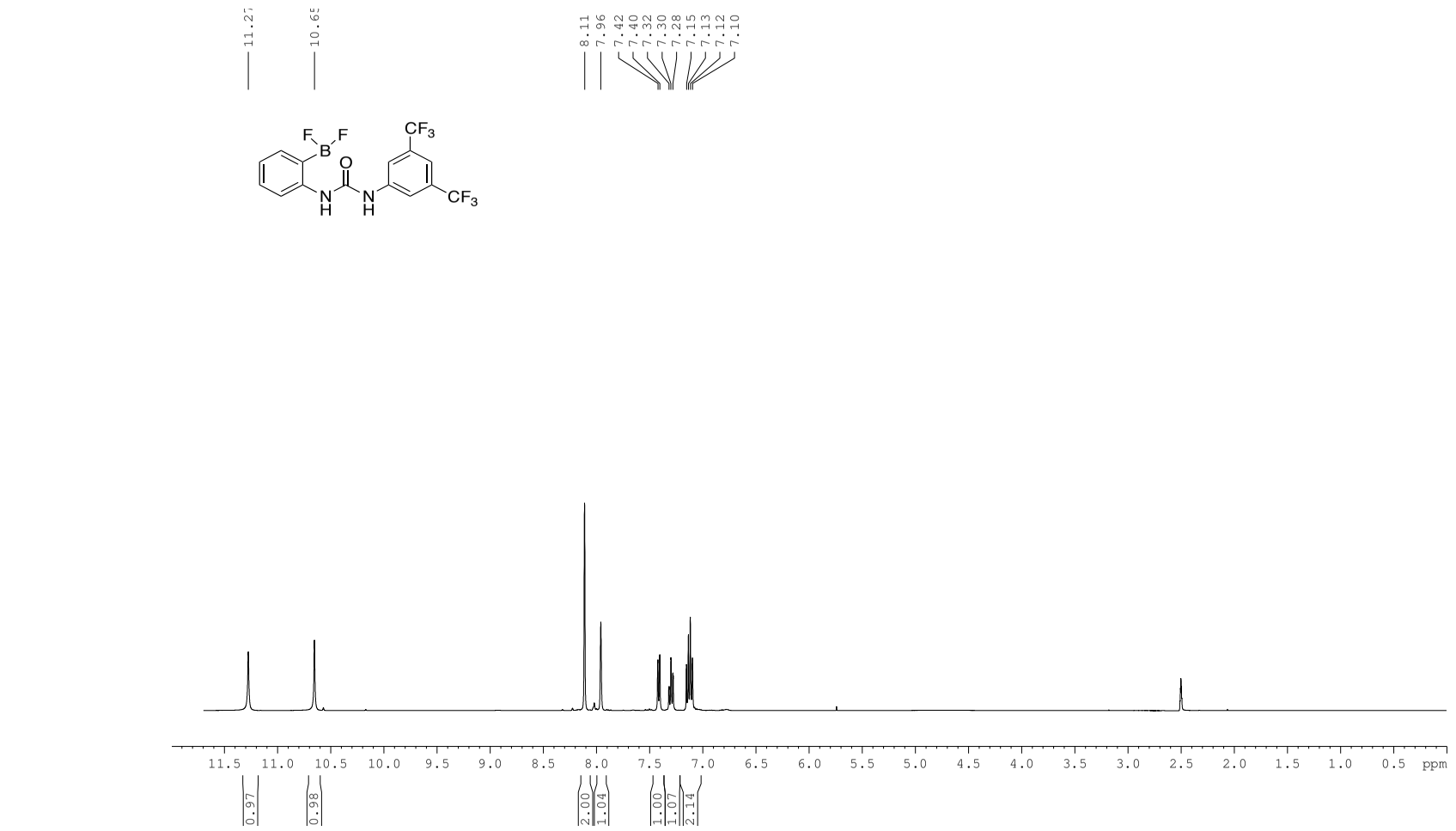
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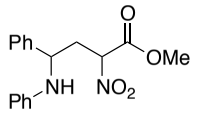
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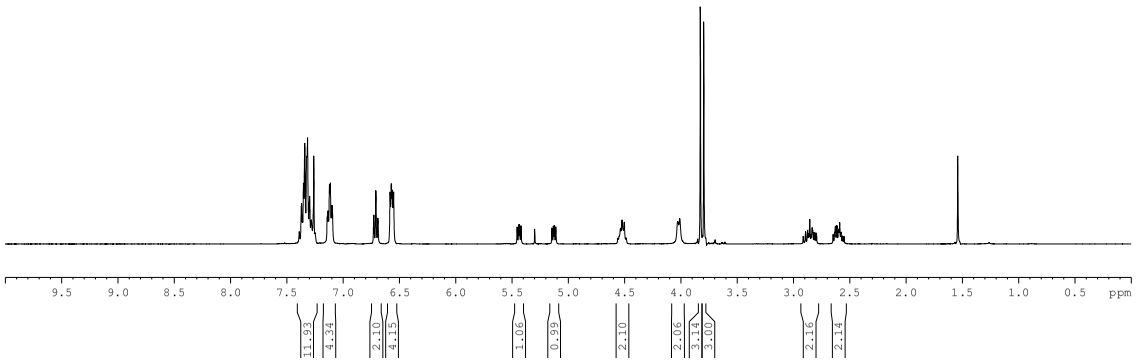
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